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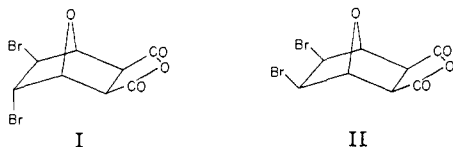
## Inert Bicyclic Vicinal Dibromides. Solvolysis, Elimination and Rearrangement Studies<sup>1</sup>

BY JEROME A. BERSON AND RONALD SWIDLER

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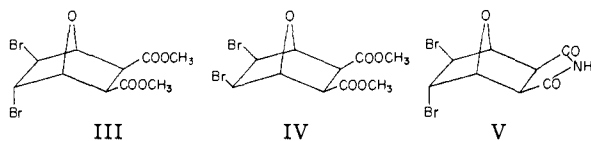
The dimethyl esters of *cis*- and *trans*-4,5-dibromo-*exo-cis*-3,6-endoxohexahydrophthalic acid and *trans*-4,5-dibromo-*exo-cis*-3,6-endoxohexahydrophthalimide survive strenuous solvolytic conditions. Neither of the esters eliminates bromine with sodium iodide in acetone and the (-)-*trans*-ester is not racemized under extreme conditions. The behavior of these substances is compared to that of model compounds and the lack of reactivity is rationalized in terms of steric and electronic factors.

The dibromoanhydrides I and II<sup>2</sup> and their derivatives provide an opportunity for investigation of the properties of vicinally substituted cyclic substances in which an unusual type of conformational<sup>3-6</sup> rigidity is imposed upon the substituents by the bicyclic system.



In this paper, we report on the highly atypical behavior of these dibromides in various reactions. While the results are not attributable entirely to steric factors, a profound modifying effect of conformational disposition on reactivity is implied.

**Reactivity in Displacement Reactions.**—Derivatives of I and II exhibit an inertness toward *solvolytic* displacement which is comparable to that of the least reactive halides known. The dimethyl esters (III and IV) survived prolonged boiling with silver bromide in acetone, silver nitrate in methanol and silver acetate in acetic acid, and the imide V



- (1) Taken in part from the Ph.D. dissertation of Ronald Swidler.
- (2) J. A. Berson and R. Swidler, *THIS JOURNAL*, **76**, 4060 (1954).
- (3) C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, **69**, 2488 (1947).
- (4) C. W. Beckett, N. K. Freeman and K. S. Pitzer, *ibid.*, **70**, 4227 (1948).
- (5) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).
- (6) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

was recovered unchanged after many hours in boiling 80% ethanol. The solvolysis results are summarized in Table I.

TABLE I  
SOLVOLYSIS EXPERIMENTS WITH DERIVATIVES OF 4,5-DIBROMO-3,6-ENDOXOHEXAHYDROPHthalic ANHYDRIDES

Halide	Reagent	Time, hours	Reaction, %	Starting material recovered, %
III	AgBr, acetone <sup>f</sup>	7 <sup>a</sup>	..	90
IV	AgBr, acetone <sup>g</sup>	12 <sup>a</sup>	..	96
III	AgOAc, HOAc <sup>h</sup>	53 <sup>a</sup>	0 <sup>a</sup>	58
III	AgNO <sub>3</sub> , MeOH <sup>i</sup>	456 <sup>b</sup>	0 <sup>d</sup>	93
IV	AgNO <sub>3</sub> , MeOH <sup>j</sup>	53 <sup>a</sup>	0 <sup>d</sup>	100
V	80% EtOH <sup>k</sup>	48 <sup>a</sup>	0 <sup>a</sup>	75

<sup>a</sup> At reflux. <sup>b</sup> Nine hours at reflux, 447 hours at room temperature. <sup>c</sup> The solid material remaining at the end of the reaction (silver acetate) was completely soluble in 6 *N* nitric acid. <sup>d</sup> As determined by the absence of silver bromide. <sup>e</sup> An aliquot failed to give a precipitate with silver nitrate in nitric acid. <sup>f</sup> Halide, 1.9 g.; AgBr 1.0 g.; acetone, 40 cc. <sup>g</sup> Halide, 2.0 g.; AgBr, 1.0 g.; acetone, 45 cc. <sup>h</sup> Halide, 1.0 g.; AgOAc, 0.5 g.; HOAc, 35 cc. <sup>i</sup> Halide, 2.0 g.; AgNO<sub>3</sub>, 2.0 g.; MeOH, 60 cc. <sup>j</sup> Halide, 1.0 g.; AgNO<sub>3</sub>, 1.0 g.; MeOH, 30 cc. <sup>k</sup> Halide, 1.0 g.; 80% (by volume) EtOH, 50 cc. <sup>l</sup> Identified by mixed melting point.

While the failure to observe reaction does not allow quantitative determination of the reactivities of these halides, we have calculated approximate maximum values for the rate constants of the reactions of Table I by assuming the solubility of silver bromide in the solvents used to be the same as that in water. In 80% ethanol solvolysis at reflux (*ca.* 80°), isobornyl chloride<sup>7</sup> and bornyl

(7) Rate constants for these substances were obtained by extrapolation from literature values [S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall, *THIS JOURNAL*, **74**, 1127 (1952)].

chloride<sup>7</sup> are, respectively, at least  $10^{10}$ – $10^{11}$  and  $10^5$ – $10^6$  times as reactive as V. While rates of silver ion-assisted solvolyses are not strictly comparable because of complications arising from heterogeneity,<sup>8</sup> bornyl chloride<sup>9</sup> appears to be at least  $10^7$ – $10^8$  times as reactive as IV toward alcoholic silver nitrate.

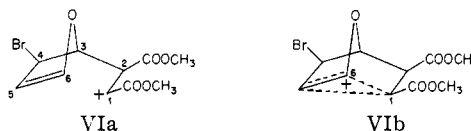
The inertness to solvolysis of the bromides of Table I is reminiscent of the behavior of bridge-head halides under similar conditions.<sup>9,10</sup> However, since the structures of the halides are known<sup>2</sup> with certainty and since both III and IV rapidly release bromide ion when treated with methanolic sodium methoxide, the origin of the extremely low solvolysis rates must be sought in some factor or factors other than bridge-head character of the C–Br bond.

Several structural features of the dibromides may reasonably be expected to exert a rate-retarding influence on solvolysis: (i) The inductive effects of the bridge oxygen and of the anhydride function operate in a direction unfavorable to ionization of the C–Br bond. It should be noted, however, that the proximity of the bridge oxygen to the reaction site is itself insufficient to account for the lack of reactivity. Thus, the dimethyl ester of a dibromide<sup>11</sup> of *exo-cis*-3,6-endomethylene- $\Delta^4$ -tetrahydrophthalic anhydride is also inert to methanolic silver nitrate for many hours.

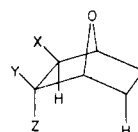
(ii) Little driving force to release of bromide ion from either the *cis*- or *trans*-dibromides is to be expected from participation of the neighboring bromine atom, since the favored coplanar-*trans* disposition of the bromines is difficultly achieved in the bicyclic system. In this case, by analogy to the observed<sup>12</sup> retardation of solvolysis rate associated with the presence of a neighboring, non-participating electronegative group, the neighboring bromine would be expected to depress the rate of solvolysis. For example, retardation of the rate of acetylation of cyclohexyl *p*-bromobenzenesulfonate by neighboring, non-participating acetoxy or *p*-bromobenzenesulfonyloxy groups amounts to a factor of the order of  $10^3$ – $10^4$ . It seems reasonable to anticipate an effect of this magnitude in the bicyclic cases at hand.<sup>13</sup>

(iii) The release of *exo*-halide or sulfonate from certain bicyclic systems is aided kinetically by participation of neighboring carbon.<sup>7</sup> In our cases, however, delocalization of the C<sub>1</sub>–C<sub>6</sub> bonding electrons presumably would not contribute as efficiently to this process as in the cases previously studied. For example, it seems likely that the

mobility of these electrons would be severely impaired by the inductive effect of the carbonyl group attached to C<sub>1</sub>.<sup>2</sup> Also, the contribution of structure VIa to the hypothetical mesomeric species VIb would be small because the positive charge is adjacent to a carbonyl group. Formation of VIb would consequently be less favorable than formation of a similar cation lacking the carbonyl function.



Factor (iii) considered alone can have no rate-depressing influence on the solvolysis of III, IV and V compared to that of bornyl chloride (*endo*-configured halogen). The observed minimum differences in rates of solvolysis between bornyl chloride and these substances (factors of at least  $10^5$ – $10^6$  for solvolysis in 80% ethanol and  $10^7$ – $10^8$  for solvolysis in silver nitrate–methanol) must then be explained in terms of the considerations (i) and (ii) above or in terms of other, previously unconsidered factors. It seems doubtful that (i) and (ii), although they operate in the desired direction, would be capable of accounting for the enormous differences in reactivity within an order or two of magnitude. A possible additional factor depends upon the unique geometry of the bicyclic system. Ionization of an *exo*-bromine (Y from VIIa for example) will receive less than the usual aid from back-side intervention of solvent<sup>14</sup> because of the hindrance provided by the *endo*-hydrogens.



VIIa, X, Y = Br; Z = H  
b, X, Z = Br; Y = H

(This situation is not encountered in the more flexible open-chain and monocyclic derivatives and is of minor importance in those bicyclic cases<sup>7</sup> in which ionization is greatly facilitated by *internal* carbon participation.) A similar argument applies to ionization of *endo*-bromine (Z in VIIb, for example), in which the adjacent *exo*-bromine and the bridge oxygen provide hindrance to back-side approach of solvent. Thus, while no quantitative estimates can be made at present, it seems likely that at least a part of the origin of the inertness to solvolysis of the bromides III, IV and V is attributable to steric factors.

#### Reactivity in Elimination and Rearrangement.—

Although derivatives of III and IV suffer facile debromination to olefins with zinc and acetic acid,<sup>2</sup> elimination is not effected by sodium iodide in acetone, even after days at reflux. The sluggishness toward iodide ion is not unexpected, since achievement of the preferred *trans*<sup>15</sup> planar four-

(8) E. D. Hughes, C. K. Ingold and S. Masterman, *J. Chem. Soc.*, 1236 (1937); W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *ibid.*, 1243 (1937).

(9) P. D. Bartlett and L. H. Knox, *THIS JOURNAL*, **61**, 3184 (1939).

(10) (a) P. D. Bartlett and S. G. Cohen, *ibid.*, **62**, 1183 (1940); (b) P. D. Bartlett and E. S. Lewis, *ibid.*, **72**, 1005 (1950); (c) W. E. Doering and E. Schoenewaldt, *ibid.*, **73**, 2333 (1951).

(11) D. Craig, *ibid.*, **72**, 4889 (1951).

(12) S. Winstein, E. Grunwald and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

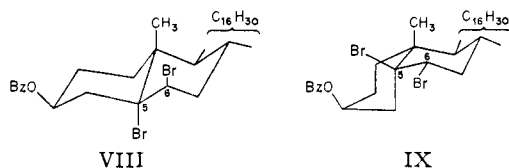
(13) It is of interest that neighboring bromine contributes a substantial driving force in the cyclopentyl system [S. Winstein and R. M. Roberts, *ibid.*, **75**, 2297 (1953)] despite the geometrically unfavorable disposition of vicinal groups compared to that in cyclohexyl or open-chain cases. The analogy to our work is only approximate, however, because of the much greater rigidity of the bicyclic system.

(14) (a) E. Grunwald and S. Winstein, *THIS JOURNAL*, **70**, 846 (1948); (b) S. Winstein, E. Grunwald and H. W. Jones, *ibid.*, **73**, 2700 (1951).

(15) S. Winstein, D. Pressman and W. G. Young, *ibid.*, **61**, 1645 (1939).

centered<sup>16</sup> transition state configuration requires enormous distortion of the bicyclic system, even in the case of the *trans*-dibromide III.

A similar situation applies in tests of the optical stability of III. A number of steroidal dibromides have been observed to suffer mutarotation in solution or in the molten state.<sup>17-20</sup> A typical example<sup>16,18</sup> is the mutarotation of 5 $\alpha$ ,6 $\beta$ -dibromocholestanyl benzoate (VIII) to a mixture of VIII and the 5 $\beta$ ,6 $\alpha$ -isomer (IX).



The transformation involves internal<sup>18</sup> rearrangement of the bromines resulting in inversions at both C<sub>5</sub> and C<sub>6</sub> as well as establishment of *cis*-locking of rings A and B of the steroid skeleton. Conformationally, a *trans*-polar-polar dibromide<sup>21</sup> (VIII) is converted to a *trans*-equatorial-equatorial<sup>21</sup> dibromide (IX). An analogous internal rearrangement of the bromines of one enantiomer of our bicyclic dibromide III would result simply in conversion to the mirror image and attendant racemization. We have investigated the optical stability of (-)III in boiling ethylene bromide (b.p. 130°) and in boiling *p*-cymene (b.p. 175°) for 82 and 252 hours, respectively. In each case, the optical activity of the test solutions remained unchanged within experimental error. Further, the (-)-anhydride (I)<sup>2</sup> survived heating in the molten state at 190° for 25 minutes without loss of optical activity. This extreme optical stability cannot be due entirely to conformational rigidity. Thus, although the conformational relationship of the bromines of IX is the same as that of the bromines of III, the rate of conversion of IX to VIII in benzene at 80° (estimated<sup>18</sup> from the equilibrium constant for the reaction VIII  $\rightleftharpoons$  IX) is  $4.3 \times 10^{-4}$  sec.<sup>-1</sup>. In the case of III, assuming the degree of racemization to be equal to the extremes of experimental error, the first-order rate constant in *p*-cymene at 175° is not greater than about  $2 \times 10^{-8}$  sec.<sup>-1</sup>. If a fac-

tor of *ca.* 10<sup>-3</sup> is applied to correct<sup>22</sup> this figure to a rate at 80°, the ratio of the rearrangement rates for IX and III is about 10<sup>7</sup>. The fact that the extraordinary resistance of III to C-Br cleavage under solvolytic conditions is paralleled by extreme optical stability supports the suggestion<sup>17</sup> that ease of heterolysis is an important factor in the facility with which vicinal dibromides suffer internal rearrangement.

### Experimental

**Solvolysis Runs (Table I).**—Silver bromide was a freshly precipitated and dried preparation. Silver acetate was commercial reagent grade, as were acetone and methanol; 80% (by volume) ethanol was made up by diluting commercial "absolute" ethanol with distilled water. Recovery of starting materials was accomplished by filtration of insoluble material and evaporation of the solvent. Silver acetate was removed by solution in 6 *N* nitric acid.

**Effect of Sodium Iodide on the Dibromides.**—A mixture of 0.5 g. of III<sup>2</sup> and 4 g. of sodium iodide in 25 cc. of acetone was heated at reflux for seven days. At the end of this time, the solution failed to develop color when starch was added. By working up the reaction mixture, 74% of the starting material was recovered. The same experiment was performed using IV. No iodine was produced and 65% of the starting material was recovered.

**Attempted Racemizations.**—A solution of 0.102 g. of (-)-III<sup>2</sup> in 20 cc. of dry, redistilled ethylene bromide was heated at reflux. Aliquots of the solution were withdrawn from time to time for polarimetry. The times and observed rotations (taken at room temperature) were: 0 hours,  $-1.24 \pm 0.01^\circ$ ; 8 hours,  $-1.23 \pm 0.02^\circ$ ; 26 hours,  $-1.23 \pm 0.02^\circ$ ; 53 hours,  $-1.21 \pm 0.01^\circ$ ; 82 hours,  $-1.22 \pm 0.02^\circ$ . The solvent was evaporated and the residue crystallized from Skellysolve B to give the ester, m.p. 75-78°, alone or mixed with starting material.

A solution of 0.101 g. of (-)-III in 20 cc. of redistilled *p*-cymene was heated at reflux. The polarimetric readings were: 0 hours,  $-1.01 \pm 0.01^\circ$ ; 8 hours,  $-1.01 \pm 0.01^\circ$ ; 123 hours,  $-1.00 \pm 0.01^\circ$ ; 282 hours,  $-1.02 \pm 0.02^\circ$ .

A sample (0.152 g.) of (-)-I<sup>2</sup> [ $\alpha$ ]<sub>D</sub> -9.6° (dioxane), was heated in an oil-bath at 190° for 25 minutes. The melt was cooled and taken up in dioxane. This solution showed [ $\alpha$ ]<sub>D</sub> -9.6°.

**Effect of Sodium Methoxide on III and IV.**—A solution of 1.0 g. of III in 25 cc. of methanol (predried over magnesium methoxide) containing sodium methoxide (from 0.5 g. of sodium) was heated at reflux for 2.5 hours. The solution gave a strong test for bromide ion with silver nitrate-nitric acid.

A suspension of 1.1 g. of IV in 50 cc. of methanol containing sodium methoxide (from 0.07 g. of sodium) was allowed to stand at room temperature for two hours. An aliquot gave a strong test for bromide ion with silver nitrate-nitric acid. The remainder of the reaction mixture was concentrated to dryness, the residue taken up in water and extracted with chloroform. Evaporation of the chloroform solution left a colorless oil which was saturated to potassium permanganate in acetone. The nature of this material is under investigation.

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(22) The difference in dielectric strength between benzene and *p*-cymene would be expected to have only a minor effect.<sup>17</sup>

(16) (a) D. H. R. Barton and E. Miller, *THIS JOURNAL*, **72**, 1066 (1950); (b) S. J. Cristol and N. L. Hause, *ibid.*, **74**, 2193 (1952).

(17) (a) J. Mauthner and W. Suida, *Monatsh.*, **15**, 91 (1894); (b) J. Mauthner, *ibid.*, **27**, 421 (1906).

(18) C. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).

(19) H. Bretschneider, Z. Foldi, F. Galinowsky and G. Fodor, *Ber.*, **74**, 1451 (1941).

(20) G. Fodor, *C. A.*, **44**, 4018 (1950).

(21) This conformation is assigned with respect to ring B.